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(58) Field of search C2C

(54) Pyrimidine compounds for the growth of hair and cosmetic formulations containing such compounds

(57) New salts of general formula I:

in which R represents hydrogen or an $SO_3^{(-)}$ group; R_1 represents a piperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hyroxypipidin-1-yl or 4-carboxybutylamino grouping, with the condition that, when R is hydrogen, R_1 is not piperidin-1-yl; when R is hydrogen A represents a compound of acid nature, selected from the group which comprises N-acetyl cysteine, thiosalicylic acid, S-carboxymethyl cysteine and 2-benzoymercapto-propionylglycine; when R is an $-SO_3^{(-)}$ group, A represents, on the contrary, a compound of basic nature, selected from the group which comprises arginine, methyl cysteine, lysine or the dimethyl ester of the carboxy-cysteine; and groups A derived from amino acids may be in the L, D or D, L form, are useful as activators for the growth of hair and for the treatment of different forms of alopecia.

Processes for the preparation of the free pyrimidines (I) are also claimed.

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SPECIFICATION

Compounds for the growth of hair and cosmetic formulations containing such compounds

5 The present invention relates to novel salts useful as activators for the growth of hair, a process for the preparation of the said salts and the formulations which contain them as active ingredients.

Products are already known which have been proposed for the treatment of changes of the scalp, these having an influence on the aesthetics of the person. Even if they have a doubtful result as regards the conservation of the head of hair, these products provide advantages in counteracting alopecia, baldness and seborrheic

10 conditions, when they are employed at the time of the commencement of the pathological manifestations. The formulations of such products are compounded with a hydro-alcoholic-glyceric medium which is balanced so as to favour the activity of the active ingredients, formed by active ingredients such as camphor, thymol, colloidal sulphur, resorcin, quinine salts, pilocarpine, acetyl resorcin, bactericides, fungicides and microergics (Vitamin A, Vitamin B_B, pantothenic acid, oestrogens, placentary extracts, heparinoids).

15 In the cosmetic filed, there are also used other products capable of intervening in respect of damage to the hair follicle due to aesthetic treatments (permanent waving, bleaching, dyeing) or related to constitutional or ambient factors.

These products, of which the efficacy has been insufficiently documented, comprise first of all the proteic lysates of prolamines and scleroproteins (horny material, hair, feathers, collagen, horsehair) which, on account of the affinity for the elements of cornea production, act by forming a compensatory thin layer, capable of repairing mechanically the processes of wear. From a therapeutic point of view, the existing formulations have to be considered as means which have a simply symptomatic signification or a generally preventive effect.

A topical or local effect on the scalp has recently been shown in the case of a known medicament with a cradio-vascular effect, this being Minoxidyl or 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine 25 (U.S. Patent No. 3382247).

The present invention is concerned with salts of the general formula I:

(T)

in which R represent hydrogen or an $SO_3^{(-)}$ group; R_1 represents a piperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl or 4-carboxybutylamino group, with the condition that, when R is hydrogen, R_1 is not piperidin-1-yl;

45 When R is hydrogen A represents a compound of acidic nature, selected from the group which comprises N-acetylcysteine, thiosalicyclic acid, S-carboxy-cysteine and 2-benzoylmercapto-propionylglycine; when R is an -SO₃⁽⁻⁾ group, A represents, on the contrary, a compound of basic nature which is selected from the group which comprises arginine, methyl cysteine, lysine or the dimethyl ester of carboxy-cysteine; and A groups derived from amino acids may be in the L, D or D,L form.

Compounds I have shown a stimulating activity for the growth of hair.

The components having a pyrimidinic structure in the salts forming the subject of the present invention, i.e. 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-piperidinol) pyrimidine, 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-piperidinol) pyrimidine, 6-amino-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine and 2,6-diamino-4-(1-piperidinyl)-1-(sulphoxy) pyrimidine, are the metabolites of Minoxidyl and are deprived of activity on the vascular system, with the exception of the 2,6-diamino-4-(1-piperidinyl)-1-(sulphoxy) pyrimidine.

It has now surprisingly been found that all the metabolites retain the same activity on the hair as that of Minoxidyl and that the novel salts of the metabolites forming the subject of the present invention show an action superior to that given by Minoxidyl by itself, in equivalent quantities, in the same cosmetic formulations.

As a consequence of prolonged daily use, for 2 to 3 months, we have found that the cosmetic formulations of 60 the invention make it possible to obtain satisfactory responses in the treatment of different forms of alopecia and in the control of the functional states of "scaling" of the hair structures which cause the progressive process of the balding.

The novel salts which are the subject of the invention are conveniently added, in proportions between 0.2 and 10%, to balms, shampoos, creams and lotions, either individually, or mixed or combined with other active 65 substances. As well as cosmetic formulations, the invention also seeks to provide processes for obtaining each

pyrimidine

compound and its novel salts. The inactive metabolites may be obtained by reaction of 4-chloro-2,6-diaminopyrimidine with 3- or 4-hydroxy-piperidine or 5-sminopentanoic acid in excess, followed by an oxidation with hydrogen peroxide in a methanolic solution, this giving the corresponding N-oxides which, by being heated at 60°, are transformed into 5 the desired hydroxy derivatives. The sulphonated active metabolite (R = SO ₄ °, R, = 1-piperidinyl) is obtained by the reaction of the Minoxidy in pryidine with chlorosulphonic acid at a temperature not above 5°. By distillation of the pyridine, acidification and treatment with acetonitrile, there is obtained the sulphoxy derivative. According to the present invention, the salts of the non-vascactive metabolites are prepared by reaction with 10 N-acetyl cysteine, to N-c2-benzoyl thiopropionyl) glycine in a molar ratio of 1:1 in a solution or suspension in solvents which are preferably formed by the C1-C2, alcohols, possible containing water in smaller proportions, at a temperature between 10° Cand 10°C°. Cand 10°C°, cand			
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(b) 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-hydroxypiperidin-1-yl) pyrimidine 30 ml of hydrogen peroxide (30%) are added to a solution of 18 g. of the compound prepared in (a) in 100 ml of methanol; the stirring is maintained for 1 hour, the solvent is evaporated and the residue is heated at 60° for 30 40 minutes. The latter is cooled and cystallised in absolute ethanol. 15 g. of the desired product are obtained. The structure is confirmed by spectral analyses. Elementary analysis (M.W. = 225.25) C H N 45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine	35		25
30 ml of hydrogen peroxide (30%) are added to a solution of 18 g. of the compound prepared in (a) in 100 ml of methanol; the stirring is maintained for 1 hour, the solvent is evaporated and the residue is heated at 60° for 30 40 minutes. The latter is cooled and cystallised in absolute ethanol. 15 g. of the desired product are obtained. The structure is confirmed by spectral analyses. Elementary analysis (M.W. = 225.25) C H N 45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine	33	Found (A) 51.71 7.30 55.45	33
30 ml of hydrogen peroxide (30%) are added to a solution of 18 g. of the compound prepared in (a) in 100 ml of methanol; the stirring is maintained for 1 hour, the solvent is evaporated and the residue is heated at 60° for 30 40 minutes. The latter is cooled and cystallised in absolute ethanol. 15 g. of the desired product are obtained. The structure is confirmed by spectral analyses. Elementary analysis (M.W. = 225.25) C H N 45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine		(b) 6-amino-1 2-dihydro-1-hydroxy-2-imino-4-(3-hydroxynineridin-1-yl) pyrimidina	
of methanol; the stirring is maintained for 1 hour, the solvent is evaporated and the residue is heated at 60° for 30 40 minutes. The latter is cooled and cystallised in absolute ethanol. 15 g. of the desired product are obtained. The structure is confirmed by spectral analyses. **Elementary analysis** (M.W. = 225.25) **C** **			
40 minutes. The latter is cooled and cystallised in absolute ethanol. 15 g. of the desired product are obtained. The structure is confirmed by spectral analyses. Elementary analysis (M.W. = 225.25) C H N 45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine			
structure is confirmed by spectral analyses. Elementary analysis (M.W. = 225.25) C H N 45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine	40	minutes. The latter is cooled and cystallised in absolute ethanol, 15 g, of the desired product are obtained. The	40
45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine			,
45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine			
45 Calculated (%) 47.99 6.71 31.09 45 Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine		Elementary analysis (M.W. = 225.25)	
Found (%) 48.01 6.74 31.05 Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine		C H N	
Examples 2-3 Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine	45	• •	45
Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine		Found (%) 48.01 6.74 31.05	
Using the operating procedure of Example 1, but replacing the 3-hydroxypiperidine by 4-hydroxypiperidine		Formula 2.2	
		, ,	
50 and 5-annihopenation acid, there are obtained the products which are set out in the following Table.	ΕO		
	50	and o-animopenation acid, there are obtained the products which are set out in the following Table.	อบ

55	Compound	Yield Mol. in weight		ELEMENTA	ARY ANALYSIS	calc. found	55
		g.		c ·	Н	N	
	6-amino-1,2-dihydro-1-hydroxy- 2-imino-4-(4-hydroxypiperidin-	15	225.25	47.99% 48.110%	6.71% 6.81%	31.09% 31.05%	
60	1-yl) pyrimidine						60
	6amino-1,2-dihydro-1-hydroxy-	15.5	242.26	44.62%	6.66%	28.91%	
	2-imino-4-(4-carboxybutylamino)-			44.70%	6.72%	28.94%	

TABLE

10

25

EXAMPLE 4

2,6-diamino-4-(1-piperidinyl)-1-(sulphoxy)pyrimidine hydroxide

29.09 g. of 6-amino-1,2-dihydro-1-1hydroxy-2-imino-piperidino-pyrimidine are dissolved in 100 ml of pyridine. The solution is cooled to 0° and, while keeping the temperature at 0°C and while stirring, 12 g. of 5 chlorosulphonic acid are slowly added. The stirring is maintained for 1 hour at 0°, 100 ml. of water are added and the solution is distilled *in vacuo* to a reduced volume. The residue is dissolved in 50 ml of water, which contains 2% of sodium carbonate, extraction with chloroform is carried out, the aqueous solution is acidified and then it is

Crystallisation is allowed to take place at 10°, thereby obtaining 23 g. of product. The special analyses confirm 10 the structure.

Elementary analysis (M.W. = 289.3)

	<i>C</i>	Н	N	S	
Calculated (%)	37.36	5.23	24.21	11.08	
15 Found (%)	37.51	5.32	24.36	11.05	15

EXAMPLE 5

N-acetyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4 (3-hydroxypiperidin-1-yl) pyrimidine (SKM/014)

20 21.69 g. of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-hydroxypiperidin-1-yl) pyrimidine and 16.32 g. of N-acetyl cysteine are dissolved under heat in 100 ml of isopropyl alcohol. The solution is cooled, 300 ml of acetone are added and the formed precipitate is separated, this being washed with acetone and dried in an oven. About 35 g. of product are obtained. The structure is confirmed by spectral analyses.

25 Elementary analysis (M.W. = 388.44)

	C	·H	N	S
Calculated (%)	43.29	6.23	21.64	8.25
Found (%)	43.40	6.24	26.71	8.20

30 Examples 6-8

Operating as described in Example 5, but employing appropriate reactants instead of the N-acetyl cysteine, there are obtained the salts of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-hydroxypiperidin-1-yl) pyrimidine, which are set out in the following Table.

35			TABLE					35
	Reactant used	Yield in	Mol. weight	ELEMEN	TARY ANA	LYSIS	calc. found	
40		g.	_	C	H	N	S	40
40	Thiosalicylic acid	35	379.45	60.65%	5.58%	18.46%	8.45%	40
	(SKN/015)			61.56%	5.60%	18.41%	8.48%	
	S-carboxymethyl cysteine	37	404.44	41.58%	5.98%	20.78%	7.93%	
45	(SKM/016)			41.61%	5.99%	20.78%	7.99%	45
	2-benzoyl mercaptopropionyl	46	492.55%	51.21%	5.73%	17.05%	6.51%	
	glycine (SKM/017)			51.30%	5.81%	17.10%	6.53%	

N-acetyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4(4-hydroxypiperidin-1-yl) pyrimidine, SKMI018

21.69 g. of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-hydroxypiperidin-1-yl) pyrimidine and 16.32 g. of N-acetyl cysteine are dissolved under heat in 100 ml of isopropyl alcohol. The solution is colled, 300 ml of 55 acetone are added and the formed precipitate is separated, this being washed with acetone and dried in an oven. 55

About 35 g. of product are obtained. The structure is confirmed by spectral analyses.

Elementary analysis (M.W. = 388.44
-----------------------	---------------

	C	r i	/ V	J	
60 Calculated (%)	43.29	6.23	21.64	0.25	60
Found (%)	43.41	6.36	20.90	0.27	

Examples 10-12

Using the operating procedure of Example 9, but replacing the N-acetyl cysteine by appropriate reactants, 65 there are obtained the salts of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-hydroxypiperidin-1-yl) pyrimidine, 65

following Table.

ď,

which are grouped in the followin	g Table.						
		TABLE					-
Reactant used	Yield in	Mol. weight	ELEMEN	TARY ANA	LYSIS	calc. found	5
	$oldsymbol{g}.$		C	Н	N	S	
Thiosalicylic acid	35	379.45	50.65%	5.58%	18.46%	8.45%	
(SKM/019)			51.19%	5,61%	18,41%	8.42%	10
S-carboxymethyl cysteine	39	404.44	41.58%	5.98%	20.78%	7.93%	
(SKM/020)			41.62%	6.00%	20.71%	7.91%	
2-benzoyl mercaptopropionyl	46.5	492.55%	51.21%	5.73%	17.05%	6.51%	15
glycine (SKM/021)			51.31%	5.83%	17.10%	6.53%	
EXAMPLE 13							_
N-acetylcysteinate of 6-amino-1,2 23.29 g. of 6-amino-1,2-dihydr							20
acetyl cysteine are dissolved unde	r heat in 80 ml o	f ethyl alcoho	l at 95° c.s.	The solution	n thus obtai	ned is	
concentrated in vacuo to about 30		stallisation, ab	out 37 g. o	f the desire	d salt are obt	ained. The	
structure is confirmed by spectral	anaiyses.						
Elementary analysis (M.W. = 390		<u>и</u> .		A/	s		25
Calculated (%)	<i>C</i> 43.07	<i>H</i> 6.20	,	<i>N</i> 17.94	8.2 [.]	1	
Found (%)	43.12	6.18		18.05	8.28		
Fxamnles 14-16							30
Examples 14-16 Using the operating procedure of	of Example 3, bu	t replacing the	e N-acetyl c	vsteine by	appropriate r	eactants, the	30 re
Using the operating procedure of are obtained the salts of 6-amino							re
Using the operating procedure of							re
Using the operating procedure of are obtained the salts of 6-amino							re
Using the operating procedure of are obtained the salts of 6-amino following Table.		-hydroxy-4-(4	1-carboxybı		pyrimidine g		re he
Using the operating procedure of are obtained the salts of 6-amino following Table.	o-1,2-dihydro-1 Yield in	-hydroxy-4-(4	1-carboxybi	utylamino) TARY ANA	pyrimidine g LYSIS	rouped in the couped in the co	re he
Using the operating procedure of are obtained the salts of 6-amino following Table.	o-1,2-dihydro-1 <i>Yield</i>	-hydroxy-4-(4 TABLE <i>Mol</i> .	1-carboxybı	utylamino)	pyrimidine g	rouped in the calc.	re he
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid	o-1,2-dihydro-1 Yield in	-hydroxy-4-(4 TABLE <i>Mol</i> .	4-carboxybi ELEMENT C 50.25%	utylamino) TARY ANA H 5.80%	pyrimidine g LYSIS	rouped in the couped in the co	re ne 35
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used	o-1,2-dihydro-1 Yield in g.	-hydroxy-4-(4 TABLE <i>Mol.</i> weight	1-carboxybi ELEMEN	utylamino) TARY ANA H	pyrimidine g LYSIS N	rouped in the calc. found S	re ne 35
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid	o-1,2-dihydro-1 Yield in g.	-hydroxy-4-(4 TABLE <i>Mol.</i> weight	4-carboxybi ELEMENT C 50.25%	utylamino) TARY ANA H 5.80%	pyrimidine g LYSIS N 14.65%	calc. found S 8.38%	re he 35
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023)	yield in g. 36	TABLE Mol. weight 382.45	## C ## 1.16%	TARY ANA H 5.80% 5.81%	pyrimidine g LYSIS N 14.65% 14.63%	calc. found S 8.38% 8.31%	re he 35
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine	yield in g. 36	TABLE Mol. weight 382.45	ELEMENT C 50.25% 51.16%	TARY ANA H 5.80% 5.81%	pyrimidine g LYSIS N 14.65% 14.63%	calc. found S 8.38% 8.31%	35 40
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024)	yield in g. 36	TABLE Mol. weight 382.45	ELEMENT C 50.25% 51.16% 8.41% 8.45%	TARY ANA H 5.80% 5.81% 5.95% 6.01%	Dyrimidine g LYSIS N 14.65% 14.63% 17.23% 17.28%	calc. found S 8.38% 8.31% 7.8%	35 40
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl	yield in g. 36	TABLE Mol. weight 382.45	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0%	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71%	Pyrimidine g LYS/S N 14.65% 14.63% 17.23% 17.28% 14.16%	calc. found S 8.38% 8.31% 7.8% 7.8%	35 40
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-acid	yield in g. 36 37 46	TABLE Mol. weight 382.45 406.44 494.55%	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2%	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71% 5.80%	Dyvimidine g LYS/S N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18%	calc. found S 8.38% 8.31% 7.8% 7.8% 6.48% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are acid.	yield in g. 36 37 46 (methylcysteine dded to a solutio	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g.	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71% 5.80%	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18%	calc. found S 8.38% 8.31% 7.8% 7.8% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-a-	yield in g. 36 37 46 (methylcysteine dded to a solutio water. After solution water. After solution water.	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g. ubilization, the	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam a solution is	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71% 5.80%	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18%	calc. found S 8.38% 8.31% 7.8% 7.8% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are ac pyrimidine hydroxide in 100 ml of product are obtained. The structure	Yield in g. 36 37 46 (methylcysteine dded to a solutio water. After solution is confirmed being by the confirmed by the confi	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g. ubilization, the	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam a solution is	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71% 5.80%	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18%	calc. found S 8.38% 8.31% 7.8% 7.8% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are ac pyrimidine hydroxide in 100 ml of product are obtained. The structure	yield in g. 36 37 46 (methylcysteine dded to a solution water. After solution is confirmed because is confirmed because is confirmed because is solution is confirmed because in the confirmed because is confirmed because it is confirmed because in the confirmed because it is confirm	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g. ubilization, the	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam a solution is	### TARY ANA ## ### 5.80% 5.81% 5.95% 6.01% 5.71% 5.80% (SKM/026 ino-4-(1-posityophilised	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18% S) piperidinyl)-1 L 40.09 g. of	calc. found S 8.38% 8.31% 7.8% 7.8% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are ac pyrimidine hydroxide in 100 ml of product are obtained. The structure Elementary analysis (M.W. = 422)	Yield in g. 36 37 46 (methylcysteine dded to a solution water. After solution is confirmed because it is confir	-hydroxy-4-(4 TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g. ubilization, the y spectral ana	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.2% pyrimidine of 2,6-diam a solution is	### TARY ANA ## ### 5.80% 5.81% 5.95% 6.01% 5.71% 5.80% (SKM/026 ino-4-(1-pictory) is lyophilised	pyrimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18% i) iperidinyl)-1 i. 40.09 g. of	calc. found S 8.38% 8.31% 7.8% 7.8% 6.48% 6.41%	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2,4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are ac pyrimidine hydroxide in 100 ml of product are obtained. The structure	yield in g. 36 37 46 (methylcysteine dded to a solution water. After solution is confirmed because is confirmed because is confirmed because is solution is confirmed because in the confirmed because is confirmed because it is confirmed because in the confirmed because it is confirm	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) on of 28.19 g. ubilization, the	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam a solution is lyses.	### TARY ANA ## ### 5.80% 5.81% 5.95% 6.01% 5.71% 5.80% (SKM/026 ino-4-(1-posityophilised	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18% S) piperidinyl)-1 L 40.09 g. of	calc. found S 8.38% 8.31% 7.8% 6.48% 6.41% -(sulphoxy) the desired	35 40 45
Using the operating procedure of are obtained the salts of 6-amino following Table. Reactant used Thiosalicylic acid (SKM/023) S-carboxymethyl cysteine (SKM/024) 2-benzoyl mercaptopropionyl glycine (SKM/025) EXAMPLE 17 2.4-diamino-4-(1-piperidinyl)-1-19.9 g. of methyl cysteine are ac pyrimidine hydroxide in 100 ml of product are obtained. The structure Elementary analysis (M.W. = 422) Calculated (%)	Yield in g. 36 37 46 (methylcysteine dded to a solution water. After solution water. After solution is confirmed by the c	TABLE Mol. weight 382.45 406.44 494.55% sulphoxylate) or of 28.19 g. ubilization, the y spectral ana	ELEMENT C 50.25% 51.16% 8.41% 8.45% 51.0% 51.2% pyrimidine of 2,6-diam e solution is	TARY ANA H 5.80% 5.81% 5.95% 6.01% 5.71% 5.80% (SKM/026) ino-4-(1-p) i lyophilised N 16.58	Dyvimidine g LYSIS N 14.65% 14.63% 17.23% 17.28% 14.16% 14.18% S) ipperidinyl)-1 i. 40.09 g. of	calc. found S 8.38% 8.31% 7.8% 6.48% 6.41% -(sulphoxy) the desired	35 40 45

Using the operating procedure of Example 17, but replacing the methyl cysteine by appropriate reactants, there are obtained the salts of the 2,6-diamino-4-(1-piperidinyl)-1-(sulphoxy)pyrimidine which are included in the

			TABLE					_	, -
	Reactant used	Yield in	Mol. weight	1	E <i>LEMENT</i>	ARY ANAL	.YSIS	calc. found	
5		g.		(C	Н	N	S	5
	Arginine (SKM/027)	44.8	449.52		40.08% 40.01%	6.50% 6.52%	24.93% 24.96%	7.13% 7.17%	
10	Lysine (SKM/028)	41.55	416.48		13.26% 13.31%	5.81% 5.90%	20.18% 20.15%	7.70% 7.65%	10
15	Dimethyl carboxycysteine (SKM/029)	48.1	482.56		39.83% 39.88%	5.85% 5.91%	14.51% 14.59%	13.29% 13.21%	15
	EXAMPLES OF FORMULATATIONS								13
20	Example A - Shampoo Sodium lauryl ethoxylate (27%) Coconut diethanolamide (90%) Ethylene glycol monostearate Stearic diester of polyethylene glycol				600 g 60 g 20 g 20 g				20
25	Colour Perfume Preservative SMK/020-SKM/021-SKM/022 Deionised water			na s.f.	2.5 g 5 g q.s. 2.0 g				25
30	Example B – Shampoo Sodium lauryl ethoxylate (27%) Coconut diethanolamide (90%) Ethylene glycol monostearate Stearic diester of polyethylene glycol				600 g 60 g 20 g 20 g				30
35	Colour Preservative SKM/014-SKM/016-SKM/017-SKM/01 Deionised water	8-SKM/019		na s f	2.5 g q.s. 2.0 g 1000				35
40	Example C – Lotion Isopropyl myristate PEG 6000 DS Cetyl alcohol		- qi		10 g 20 g 20 g				40
45	Antioxidant Carbopol 940 10% sodium hydroxide solution EDTA Ethanol				1.0 g 1.5 g 3 ml 0.5 g 30 ml				45
50	Perfumed composition SKM/015 Deionised water		q.s	s.f.	5 g 10 g 1000				50
55	Example D – Lotion Isopropyl myristate PEG 6000 DS Cetyl alcohol Antioxidant Carbopol 940				10 g 20 g 20 g 1.0 g 1.5 g				55
60	10% sodium hydroxide solution EDTA Ethanol Perfumed composition SKM/015-SKM/0167-SKM/020 Deionised water			na s.f.	3.0 ml 0.5 g 30 ml 5 g 0.335				60

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	Example E - Lotion				
	Isopropyl myristate		10 g		
	PEG 6000 DS		20 g		
	Cetyl alcohol		20 g		
5	Antioxidant		1.0 g		5
•	Carbopol 940		1.5 g		_
	10% sodium hydroxide solution		3.0 ml		
	EDTA		0.5 g		
	Ethanol		30 ml		
10	SKM/014-SKM/015-SKM/016		50 1111		10
	SKM/017-SKM/018-SKM/109-SKM/020	ana	0.56 g		
	Deionised water		1000		
	Delottised Woto	qioin	1000		
	Example F – Balm				
15	Cetyl alcohol		25 g		15
15	Solulan		25 g 10 g		13
	Quarternary ammonium		10 g		
	Nesatol Siliconos		10 g		
20	Silicones		5 g		20
20	Monopropylene glycol Glicam P 10		10 g		20
			10 g 30 g		
	PEG 6000 DS		-		
	Preserving mixture		5 g		
25	Perfume		4 g		25
25	SKM/022-SKM/023-SKM/024-SKM/025	ana	2.5 g		20
	Example G – Ointment				
	Cetomacrogal		18 g		
			240 g		
20	Cetyl stearic alcohol		240 g 150 g	•	30
30	Solid paraffin Liquid paraffin		•		30
	Perfume		60 g		
			q.s.		
	Preservative		q.s. 6.0		
25	Monosodium and bisodium phosphate q.s. for pH		0.0 1.0 g		35
35	SKM/026-SKM/027-SKM/028-SKM/029	ana	1.0 g		30
	Deionised water The novel salts according to the invention are provided.	•		ice which activate the functions	
	of the follicles, which are transformed into the prolongati		-		
	Local application of the compounds according to the				
40	of the hair or fur in rodents having alopecia induced by a				40
40	of the toxic treatment, the growth of the new fur in the z				40
	compared with that observed in the animals treated local				
	treated locally with equivalent quantities of Minoxidyl.	ny with Ot	nei products	in Current use of in animois	
	Another surprising observation concerns the effect wh	ich ic cha	wn by the cal	te of non-vacoactive metabolities	
AG	of which the activity, from a quantitive point of view, is s				45
40	Minoxidyl applied locally in equivalent quantities.	MIÇWII (U	DO MICIO	ise than that of the same	
	Experiments carried out on New Zealand rabbits or Bo	umoane t	ahhite have d	emonetrated that the local	
	application of the compounds according to the inventior				
	growth of the hair or fur in previously shaved cutaneous				
EΛ	spontaneous depilation in the intact cutaneous zones. In	the treate	d zonos prov	viously subjected to shaving the	50
50					-
	average speed of growth of the hair or fur is shown to be found in the untreated zones.	ร บ.อ เกเก/	ធាច, ពេល ១៩៣៩	anont 22 to Albara man mar	
		abita Tha		history and absorpted after 45.60	
	These observations were made with a sample of 80 rat			uvity was observed after 45-00	
	days of treatment with 1 mg/die of each salt in two appli			land trootment with the salts -f	55
55		urprising	enicacy in the	e local treatment with the saits of	ນວ
	non-vasoactive metabolities, which is greater than that v	Auicu Mas	snown when	i employing equivalent quantities	
	of Minoxidyl.				

CLAIMS

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1. Compounds of general formula I

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R represents hydrogen or an SO₃⁽⁻⁾ group;

R₁ represents a piperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypipidin-1-yl or 4-carboxybutylamino grouping, with the condition that, when R is hydrogen, R1 is not piperidin-1-yl;

when R is hydrogen A represents a compound of acid nature, selected from the group which comprises N-acetyl 20 cysteine, thiosalicyclic acid, S-carboxymethyl cysteine and 2-benzoylmercapto-propionylglycine; when R is an 20 -SO₃(**) group, A represents, on the contrary, a compound of basic nature, selected from the group which comprises arginine, methyl cysteine, lysine or the dimethyl ester of the carboxy-cysteine; and groups A derived from amino acids may be in the L, D or D,L form.

2. Compound according to claim 1, selected from the group constituted by:

- N-acetylcysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-hydroxypiperidin-1-yl) pyrimidine;
 - thiosalicylate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4(3-hydroxypiperidin-1-yl) pyrimidine;
- S-carboxymethylcysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(3-hydroxypiperidin-1-yl)
- 2-benzoylmercaptopropionyl glycinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-hydroxypiperidin-1-30 ' yl) pyrimidine;
 - N-acetyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine;
 - thiosalicylate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine;
 - S-carboxymethyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine;
- 2-benzoylmercaptopropionyl glycinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-hydroxypiperidin-35 1-yl) pyrimidine;
 - N-acetyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine;
 - Thiosalicylate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino) pyrimidine;
 - S-carboxymethyl cysteinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybutylamino)
- 40 pyrimidine: - 2-benzoylmercaptopropionyl glycinate of 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-(4-carboxybuty
 - lamino) pyrimidine:
 - 2,6-diamino-4-(1-piperidinyl)-1-(methyl cysteine sulphoxylate)-pyrimidine;
 - 2,6-diamino-4-(1-piperidinyl)-1-(arginine sulphoxylate)-pyrimidine;
- -2,6-diamino-4-(1-piperidinyl)-1-(lysine sulphoxylate)-pyrimidine;
 - -2,6-diamino-4-(1-piperidinyl)-1-(dimethylcarboxy cysteine sulphoxylate)-pyrimidine.
 - 3. Process for the preparation of the compounds of formula I, comprising reacting the compounds of formula:

in which R and R₁ have the meanings specified above, with the compounds A, in almost stoichiometric quantities in solution or in suspension in water C1-C4 alcoholic solvents at the boiling temperature of the solvent, and isolating the salt I by crystallisation in the partially or entirely evaporated solvent, with addition of acetone,

65 or by lyophilisation when the solvent is water.

5. Process for the preparation of the compounds of formula (Ib)

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20 in which R₁ represents piperidin-1-yl, comprising reacting 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidino-pyrimidine with chlorosulphonic acid in pyridine.

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6. Cosmetic compositions for the growth of hair and for the treatment of alopecias, containing as active ingredient, one or more compounds according to claim 1 or 2.
7. Cosmetic compositions according to claim 6, in the form of shampoos, lotions, balms, ointments or

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25 creams.
8. Compositions according to claim 6 or 7, wherein the active ingredients are present in percentages which are between 1 and 10%.

- 9. A compound according to claim 1 substantially as described herein and exemplified.
- A process for the preparation of compounds of formula I substantially as described herein and
 exemplified.

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A cosmetic composition according to claim 6 substantially as described herein and exemplified.

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